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FACSIMILE COVER SHEET

Examiner: **Shengjun Wang** **Group:** 1617

Date: August 2, 2004

Client Code: 3053

Facsimile No.: **703-872-9306**

From: Carol A. Egner, Esq.

Subject:

Paper:	Reply to Advisory Action
Docket No.:	3053.1000-001
Applicants:	Hong Xue, Hui Kwok Min, Hongyan Wang and Hui Zheng
Serial No.:	09/909,862
Filing Date:	July 20, 2001

Number of pages including this cover sheet: 4

Please confirm receipt of facsimile: Yes ___ No ___

Comments:

AOC/CAE/bmw
August 2, 2004

Docket No.: 3053 1000-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Hong Xue, Hui Kwok Min, Hongyan Wang and Hui Zheng		
Application No.:	09/909,862	Group:	1617
Filed:	July 20, 2001	Examiner:	Shengjun Wang
Confirmation No.:	8767		

For: COMPOUND FOR TREATMENT OF ANXIETY AND METHODS OF PREPARATION AND USE THEREOF

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REPLY TO ADVISORY ACTION

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following remarks are to respond to the Advisory Action mailed from the United States Patent and Trademark Office on 9 June 2004.

Claims 13-16 and 19-22 remain pending. These claims were rejected in the final Office Action mailed from the U.S. Patent and Trademark Office on 30 March 2004 under 35 C.F.R. § 103(a) on the basis of Cassels *et al.*, US 5,756,538.

Cassels *et al* teach a large class of flavonoid compounds by structure. Cassels *et al.* also teach methods of treating anxiety in a patient by administering to the patient certain flavonoid compounds.

The Examiner has sought to establish a prima facie case of obviousness (see Office Action dated 22 August 2003):

> However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to treat anxiety by employing a flavone with hydroxyl groups at 5 and 7, and a methoxyl group at position 8 (R4 as depicted by Cassels)." A person of ordinary skill in the art would have been motivated to treat anxiety by employing a flavone with hydroxyl groups at 5 and 7, and a methoxyl group at position 8 (R4 as depicted by Cassels) because Cassels expressly prefer flavone with 5 and 7 dihydroxyl groups and methoxyl group is known to be useful as a substituent at position 8 (R4). The selection of methoxyl group herein is seen to be a selection from amongst equally suitable functional groups and as such obvious. *Ex parte Winters* 11 USPQ 2nd 1387 (at 1388).

The Examiner seems to be saying that to carry out a method of treating anxiety, one of ordinary skill in the art would be able to consider the class of compounds described in Cassels *et al.* and choose among a group of compounds with similar structures. The Examiner is making the assumption that compounds of similar structures have similar anxiolytic effects.

This assumption is incorrect. Of the many possible flavonoids described by structure in Cassels *et al.*, only a few were reported to have any physiological effect. No negative results were reported, leaving one to guess at how many were tested and not found to be useful for anti-anxiety effects. Only six flavonoids were shown to have anxiolytic activity in mice. The compounds were chrysin, apigenin, 2'-chlorochrysin, 2'-fluorochrysin, 6, 8-dibromochrysin and 7-bromoflavone. The only common structural feature shared by the six flavonoids was the underlying structure of flavone. Thus, it is inherent in the art that the structure of flavonoids is not correlated with their anxiolytic function.

This inherent lack of correlation between structure and physiological function among the flavonoids is further demonstrated by Huen *et al.*, presented with the Amendment After Final as Exhibit A (Huen, M.S.Y. *et al., Biochem. Pharmacol. 66(1)*:125-132, 2003). The only structural difference between wogonin of the claims and oroxylin A is the position of the methoxyl group (at the 8 position in wogonin, and at the 6 position in oroxylin A). Like wogonin, oroxylin A is a flavonoid extracted from *Scutellaria baicalensis*. However, oroxylin A acts as an antagonist of

agents that bind at the $GABA_A$ receptor benzodiazepine binding site as agonists. Oroxylin A has no stimulant, depressive, sedative, anxiolytic or myorelaxant effects of its own. Nor does it affect motor coordination of picrotoxin-induced seizures. Oroxylin A abolishes the anxiolytic and motor uncoordination effects of diazepam, and partially counteracts the myorelaxation effect of diazepam.

The only reason why, as the Examiner suggests, "A person of ordinary skill in the art would have been motivated to treat anxiety by employing a flavone with hydroxyl groups at 5 and 7, and a methoxyl group at position 8 (R4 as depicted by Cassels) . . ." is if there had been reason to assume that a compound of such a structure would have anxiolytic effects. Cassels *et al.* gave one of ordinary skill in the art no reason to make such an assumption. There is no evidence in Cassels *et al.* that a flavonoid with substituents at the 5, 7 and 8 positions would have an anxiolytic effect, or that a methoxyl group at position 8 or any other position would produce an anxiolytic flavonoid.

Respectfully submitted,

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